

REMARKS

Reconsideration and entry of the present amendment after final is respectfully requested.

Status of the Claims:

Applicants note with thanks Examiner's correction of claim numbering. Claims 1-77 were pending after submission of Paper No. 11. Claims 2-67, and 72-77 have been cancelled. Applicants reserve the right to pursue the contents of these claims in continuing applications. Claims 1, and 68-71 remain under examination after amendment. Support for the amendments is found in the claims as originally filed, and throughout the specification. No new matter has been added.

Information Disclosure Statement:

Applicants acknowledge with thanks Examiner's initialed and dated copy of the Form 1449 IDS, Paper No. 9, filed 8 April 2003.

Double Patenting Rejection:

Claims 2-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,235,972.

Claims 2-7 have been cancelled in the current response, thereby obviating the rejection.

Rejections under 35 U.S.C. §112, 1st Paragraph, Written Description:

Claims 1-7 and 68-70 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not sufficiently described in the specification to indicate the inventor(s) had possession of the invention.

The Action asserts that Appendices A and B, submitted in Paper Number 11 filed 9 April 2003, do not clearly relate the evidence to the claimed percentages of sequence identity of SEQ ID NOS: 2 and 4.

Claims 2-7 have been cancelled in the current amendment. The rejection will be responded to regarding remaining claims 1, and 68-70. Applicants have modified the Multiple Sequence Alignment to note the conserved domains and residues as noted in Pfam portion of the BioScout analysis (Appendix B, Paper No. 11). Applicants also submit pairwise GAP analyses comparing SEQ ID NO: 2 and 4 individually to the sequences used in the Multiple Sequence Alignment. This information (modified MSA and GAPs) is submitted as Appendix C, along with the NCBI information for each sequence used in the analyses.

As shown in the GAP analyses, SEQ ID NO: 2 shares the following overall percent identities and similarities:

| SEQ ID NO: 2 vs. | Source | % Identity | % Similarity |
|------------------|----------------------|------------|--------------|
| Y12013aa | <i>D. carota</i> | 65.789 | 71.053 |
| U63530aa | <i>O. sativa</i> | 62.694 | 68.394 |
| P32628 | <i>S. cerevisiae</i> | 37.637 | 46.978 |
| P54725 | <i>H. sapiens</i> | 38.244 | 48.725 |

As shown in the GAP analyses, SEQ ID NO: 4 shares the following overall percent identities and similarities:

| SEQ ID NO: 4 vs. | Source | % Identity | % Similarity |
|------------------|----------------------|------------|--------------|
| Y12013aa | <i>D. carota</i> | 56.787 | 63.989 |
| U63530aa | <i>O. sativa</i> | 54.918 | 61.749 |
| P32628 | <i>S. cerevisiae</i> | 35.593 | 45.480 |
| P54725 | <i>H. sapiens</i> | 38.757 | 52.959 |

The present invention describes Rad23 polypeptides, involved in nucleotide excision repair, having approximately 35% - 66% sequence identity to other known Rad23 nucleotide excision repair proteins, and further comprising conserved amino acids and domains common to Rad23 polypeptides. Within the plant kingdom, the Rad23 polypeptides have approximately 54% - 66% sequence identity to other known plant Rad23 proteins. As shown by Sturm & Lienhard (1998 *Plant J.* 13(6):815-821; Ref. A10 in IDS Paper No. 9 submitted 8 April 2003), the protein encoded by Y12013 from *D. carota* (carrot) complements a Rad23 mutant in yeast.

As illustrated in the BioScout Analysis (Appendix B, Paper No. 11) and the Multiple Sequence Alignment (Appendix C) modified to highlight the known conserved domains, the polypeptides of SEQ ID NOS: 2 and 4 possess the expected domains for Rad23 in the expected positions, an N-terminal Ubiquitin domain, and two UBA domains, one centrally located, and one at the C-terminus. The 3-D structure of the C-terminal UBA domain (UBA2) from human Rad23 was determined and the P333E mutant deposited in the PDB as 1F4I.

Further, using a standard technique of Multiple Sequence Alignment (*e.g.* Appendix C), one of skill in the art could discover the evolutionary tolerance for amino acid substitutions, insertions or deletions (*i.e.* gaps) at given positions in the polypeptide. The Multiple Sequence Alignment presented in Appendix C, which could have been done by one of skill in the art at the time of filing, shows several regions conserved in Rad23 polypeptides, and also suggests locations and amino acid substitutions likely to be tolerated in both conserved and non-conserved domains. Appendix C shows individual and blocks of amino acids which are identical to the corresponding amino acid of SEQ ID NOS: 2 or 4, or similar (conservative substitutions), or not conserved.

For example, as expected the pfam|hmm|Ubiquitin domain from amino acid 1 -78 (SEQ ID NOS: 2 & 4 numbering) shows a high degree of sequence identity to other Rad23 proteins. It is also noteworthy that not all amino acids in this domain

are absolutely conserved, for example, there is a Glutamate at position 14 of SEQ ID NOS: 2, 4, and Y12013, however non-conservative amino acids Glutamine, Lysine or Proline at the equivalent position in U63530, P54725 or P32628, indicating the likelihood that the polypeptide function (involved in nucleotide excision repair) would be maintained even when Lysine, Proline, or Glutamine is substituted for Glutamate at this position. In fact, as these amino acids are not conserved substitutions, this position may be expected to be very tolerant of a wide range of residue substitutions. At amino acid 3 either Leucine or Isoleucine is found in the sequences, which are considered conservative substitutions relative to each other. This indicates that a conservative substitution (*e.g.* Valine, Isoleucine, or Methionine) for Leucine is most likely tolerated at this position, maintaining nucleotide excision repair function.

The present invention describes Rad23 polypeptides involved in nucleotide excision repair having approximately 35% - 66% sequence identity to other known Rad23 polypeptides, and further comprising conserved amino acids and domains common to Rad23 polypeptides. Using a standard technique of Multiple Sequence Alignment (*e.g.* Appendix C), one of skill in the art could discover the evolutionary tolerance for amino acid substitutions, insertions or deletions (*i.e.* gaps) at given positions in the polypeptide, and further predict the likely impact of other modifications.

Therefore, Applicants submit that the specification, coupled with the state of the art at the time of filing reasonably conveys to one of skill in the art that the inventor had possession of polypeptides having 80, 85, 90, or 95% sequence identity to SEQ ID NOS: 2 and 4 and involved in nucleotide excision repair as recited in Claims 1, and 68-70. Applicants respectfully request that the rejection of Claims 1, and 68-70 under 35 U.S.C §112, first paragraph be withdrawn.

Rejections under 35 U.S.C. §101 – Non-Statutory Subject Matter:

Claims 3, 72, and 73 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. The claims would read on a maize cell naturally comprising said polypeptide.

Claims 3, 72, and 73 have been cancelled in the current response, thereby obviating the rejection.

Rejections under 35 U.S.C. §102 – Novelty:

Claims 3-7 and 72-77 are rejected under 35 U.S.C. §102(b) as being anticipated by Lundquist et al., US 5,554,798 issued September 1996.

The Action asserts that Lundquist et al. teaches a nonhuman host cell, a transgenic maize plant (claim 8), and a monocot, comprising a polypeptide having 80, 85, 90, and 95% identity with SEQ ID NO: 2. It is asserted that Lundquist also teaches a host cell, a transgenic maize plant and seed (Table 4, col 21, and claims 1-3 and 5) comprising SEQ ID NO: 2 and 4.

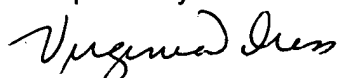
Claims 3-7 and 72-77 have been cancelled in the current response, thereby obviating the instant rejection.

Serial No. 09/805,550
Group Art Unit: 1638

CONCLUSION

In light of the foregoing remarks and amendments, it is believed that claims 1, and 68-71 are in condition for allowance. Entry of the current amendment after final, reconsideration of the application, and withdrawal of the outstanding rejections and allowance of all of the remaining claims is respectfully requested.

Respectfully submitted,



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U.S. Serial No. 09/805,550
Group Art Unit: 1638

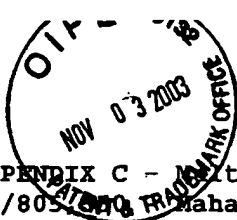


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APPENDIX C



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APPENDIX C - Multiple Alignment with conserved domains noted.
09/805/0000 Mahajan
Docket 0964D
!!AA_MULTIPLE_ALIGNMENT 1.0
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Symbol comparison table: genrundata:blosum62.cmp CompCheck: 1102

GapWeight: 8 GapLengthWeight: 2

0964DP32628_pileup_54762.txt MSF: 433 Type: P March 31, 2003 14:25 Check:
7851 ..

Y12013aa Protein encoded by GenBank Y12013, Carrot Rad23
0964sid2 SEQ ID NO: 2, Maize Rad23
U63530aa Protein encoded by GenBank U63530, Rice Rad23
P54725 SwissProt protein deposit P54725, human Rad23A
P32628 SwissProt protein deposit P32628, S. cerevisiae Rad23

Residues IDENTICAL to 0964sid2

BioScout BLASTP and Pfam HMMER domains noted by special formatting, BioScout
analysis presented in Appendix B of Paper No. 11 submitted 9 April 2003

```
1 50
Y12013aa ~MK YVKEI KG EETQ N PDDSVADVKR SRET OGA V YPAACOMITD
0964sid2 ~MGNNVGNP KG EETAS PDASVADVKR TRET OGS YPAACOMITD Ubiquitin
U63530aa ~MK SVGEL KG TQIE SAQKVADVKR TRET OCHI YPAACOMITD
P54725 ma t t k e l q q t t k r p d e y k v k e k e k e r d p v a g g k l y
P32628 ~m s i t f k n f k e k v p d p s n l t k t k . . . s i s c . e e s g i k l y

51 100
Y12013aa QGK IRGDT ELENVAENS F VIMISK R PSGEGST TAAAPK PQT
0964sid2 QGK IRGDT ELENVAENS F VIMISK R ASSSGAST TAKAPA LQ
U63530aa QGK IRGDT ELENVAENS F VIMIRQGR GSSSSAP KAPNQ PPT
P54725 a g k l s d v p r d y r d e k n f v m k k a g g g t p p e p p a a p e s
P32628 s g k l q d s k e l s e c g k g d q v f m g q k k . . . . . k v l e p p i p e s

101 150
Y12013aa SAPESVPAP V QPE S L P V P S P A E . . . A P A A H I P A A V G S A N V Y
0964sid2 P A A R V A P A V R T P T Q A . P V A E A P P V O R Q A P A A V A D A D V Y
U63530aa Q V E A A P A Q A P V A P T V P V V A P E T T . . . A P A P V A V S A A N Y
P54725 t f p a p a g h p p a a r e d k p s e e s a p t t s p e v g p p g s g r e
P32628 a t p g r e n . . . . . l e a s p s i d a s a p a t a p e g p p q e e q t t e r t e

151 200
Y12013aa DSAASLI VAG SMISG IQQI LDMGGGTR R DIV RI RAA NNPRRA Y
0964sid2 S O A S N I A V G S N N I R Q T I Q Q I L D M G G G T R R D I V R I A R A A Y N N P R R A Y
U63530aa G O A S N I A V A G S N I R A T I Q S I L M G G G I V R D I V H A I S A A N N P R A Y
P54725 e d a a s t l y t g s e y e t m t e l s n g . . . . . e r i r v a a l r a a n n p h r a y
P32628 s a p g f v v g t e r n e t l e r l m g . . . . . q l l e v e r a l r a a n n p r a y

201 250
Y12013aa I N S G I P E A E A P P V A P P P G . . . . . O A A N E L D O P P A A . . A O P P A S A G E
0964sid2 I N S G I P E A E A P V A R P A A G Q Q N Q A A S P A . O P A V A L P V O P S A S A G E
U63530aa I N S G P R I . P V . . P E P I O P N P T Q A S Q A T O P A A . . . . P S I L S G P
P54725 l l g p . . . . . g s p e p e h g s v d e q v l e a p a . . . . .
P32628 l l m g p e n r q p e p q q q t a a a a e q p s t a a t l e a p a e d d l f . . q a q g g
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UBA/TS-N

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| | | | |
|----------|---|--|--------------------|
| | 251 | | 300 |
| Y12013aa | NANPDLRPO G RDMGSN... ..AAG ENL DFRTNQOFO ALRA VO NE | | |
| 0964sid2 | NANPDLRPO G P GGSNPG VVPGAG CAL DAIR LPOFO ALLLOVOANT | | |
| U63530aa | NANPDLRPO A PNAS ID... ..AAGLGNI DAIR NAQER LLSLVQANT | | |
| P54725 |teaagenp firdqpfq nrg gnp | | |
| P32628 | nassgaigtg gga da gg ppgsigltve dld..... lrg vsghp | | |
| | 301 | | 350 |
| Y12013aa | QILOPMLQEL GKONPH RL IOEHOA ELQ LNEPM..... | | |
| 0964sid2 | QILOPMLQEL GKONPH RL IOEHOA ELQ LNEPM..... | | |
| U63530aa | QILOPMLQEL GKONPH RL IOEHOA ELQ LNEPM..... | | |
| P54725 | a lpa lqg qgenp lqq lsrhgeqf q neppg... ..el | | |
| P32628 | eallap len saryp reh imanpevis s le vgdnm qdvmegaddm | | |
| | 351 | | 400 |
| Y12013aa | .EGGE..N L GH....GPO. V TPEER LATER LEAMGFDREL | | |
| 0964sid2 | .EGGPGGN L COLAAA PO T... V TPEER LATER LEAMGFDREL | | UBA2 domain |
| U63530aa | .EGDDEEN L DQFPEA PO T... V TPEER LATER LEAMGFDREL | | (BLASTP 1F4I) |
| P54725 | a lsdvege gaigeeapd.mny qg lqge laker lka gfpesl | | |
| P32628 | vegedievtg eaaaag ggg egeg fgd y tpeddqa lsr lce gfer l | | |
| | 401 | | 433 |
| Y12013aa | VLEVFACNR NEEL ANYLL DHMHERE~ ~~~ | | |
| 0964sid2 | VLEVFACNR DEEL ANYLL DHCHSDQ QQ~ | | UBA/TS-N (HMMPFAM) |
| U63530aa | VE VERA CNK DEOL ANYLL DHMREADE GPP | | |
| P54725 | v qa lade nenl an l s...qnfode ~~~ | | |
| P32628 | v qv facdk neea anilf sdnad~~~~ ~~~ | | |



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APPENDIX C - Multiple Alignment with conserved domains noted.
09/805,550 - Mahajan
Docket 0964D
!!AA_MULTIPLE_ALIGNMENT 1.0
FileUp of: @/tmp/54847313.list

Symbol comparison table: genrundata:blosum62.cmp CompCheck: 1102

GapWeight: 8 GapLengthWeight: 2

0964DP32628_pileup_54847.txt MSF: 424 Type: P March 31, 2003 14:40 Check:
7143 ..

U63530aa Protein encoded by GenBank U63530, Rice Rad23
Y12013aa Protein encoded by GenBank Y12013, Carrot Rad23
0964sid4 SEQ ID NO: 4, Maize Rad23
P54725 SwissProt protein deposit P54725, Human Rad23A
P32628 SwissProt protein deposit P32628, S. cerevisiae Rad23

Residues IDENTICAL to 0964sid4:

BioScout BLASTP and Pfam HMMER domains noted by special formatting, BioScout analysis presented in Appendix B of Paper No. 11 submitted 9 April 2003

```

1                                     50
U63530aa  ~MK VKTL KG TFQIEVD SAQK ADVK ILETTOGQHI YPAEQO LIH
Y12013aa  ~MK YVKHL KG QFETQV PDE ADVK SIETAOGAAV YPAEQO IIT
0964sid4  ~MGTVIGTL KG HFFETRV PNDPL AVK NIKEIQG D YPWCQO IIT Ubiquitin
P54725    ma t t ktl qqtifkire pd t kv ke kicaekg d pvagqkl
P32628    ~m sltfknf kkekvp de psnt letkt kaqsiscee ...sqikll

51                                     100
U63530aa  GKVLKD T L ENKVLENS FLV MLRQGK GSSS APATS K PSN PPT
Y12013aa  GKVLKDG T L LENNVARN S F V MLSSKSK PSGEGSTTS AAPK POT
0964sid4  GKVLKD T L ENKVLNKG FLVVMSSKSK SGSTG..TS SQH P T
P54725    agk lsd vp r y dekn f vvm ktk ggqtsappe spt ape
P32628    sgkvlqskt secg k gd q vfm sqkk k.....tk v eppi pe

101                                    150
U63530aa  QTVPAAPAS. QAPVAPA... .TVP TVSAP TPTA A PAP AVAVSSEADN
Y12013aa  SAPPS PAP. AVSOPPA... .TLF P PSP APAPATAPIP SAAVGSEANV
0964sid4  RQ PP EAPQ QAPQPEVA... .P T SQP EGLPAQAP... ..NT
P54725    tsfpap sg m hpppaare dkspsaesap ttsp.e vsg svpssgssgr
P32628    at pgrenst eas..ps da saapa. ap egspqgeeqt attertes..

151                                    200
U63530aa  YG A SNL GSN T I S EMGGGIWD DIVLHALSA A NNPERAVE
Y12013aa  YDSAASLI GSN GAI Q MGCG WD DTVIRI RA A NNPERAVE
0964sid4  HD AASNL GRNV T I Q MEMGGG WD D VQRAIRA AYNPERAVE UBA/TS-N
P54725    e daastl gsey t te msug... vvaalra lymphave
P32628    ..a pgf v gternetier meng... q everalra a nnp rave

201                                    250
U63530aa  YLYSG PEQM IP..VP.PP SIQPANPTQA SQATOP AP ILSSGPN P
Y12013aa  YLYSGIPEQA EAPPVAPSEP SGQAANPLDQ PPAAAPAPA ..SAGPN NP
0964sid4  YLYSGLEVTA EI....AVPI GGQGAN TDR ....AP G A GLSGIPN P
P54725    yll gip... ..gspepe hgs....vqe sqvseqpa.. .....
P32628    yllmgipenl rqppeqqqta aaagp taa ttaeqp e d lf qaa ggn
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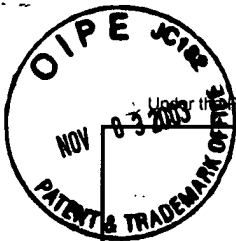
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U63530aa LDLEFQALPN ASTDAAGLGN LDAL RNNAO FR LS VO NPQILQF IQ
Y12013aa LDLEFQGLPD MGSNAAGAGN LDLE RTNQQ FOA RAMVO NPQILQPMIQ
0964sid4 LDLEFQGG N AGGGAGG GP LDLE RNNPQ FOA REMVE NPQILQPMIV
P54725 ..... ..teaagenp l fl rd pg fgn rq qq npa lpa lq
P32628 assgalg g gatdaagggp pgs gltved ll rd vsq npealap le

301                                     350
U63530aa ELGKONPOIL QLIQENQAEF LHL NEP... ..ARGD E .
Y12013aa ELGKONPH RLQEHQA F IQL NEP... ..MEGG...
0964sid4 ELGKONPOIL RLIEENH KT IQL NEP... ..FECC G .
P54725 qlgqenp l qlsrhq qf q lneppg. .... ela is v .
P32628 n saryp r ehimanp vf s illeavgd nmqdvme gad dmvege i v

351                                     400
U63530aa ....NLLDQF PEAMPO... I VTPPEDEAL LRLEPMGFDR ALV VEFAC
Y12013aa ....NLLGHG PQA..... I SVTPPEER AJ ERLE MGEDR ELV EEFAC
0964sid4 ....FLDQPE E ENPH... I SVTPPEQKAI GRLE MGEDR ARVIEATLAC UBA2 domain
P54725 ....gevgai g eapqmyi qvtpqekeai erlk g fpe lviqa fac (BLASTP 1F4I)
P32628 tgeaaaaglg qgegeg fq dytpe dqai srlice g f r dlviqv fac

401                                     424
U63530aa N DEQLAANY LL HMNEFAD EGPP
Y12013aa N NEELAANY LL HMHEF ~ ~~~~
0964sid4 D NEELAANY LL HAGE ~ ~~~~ UBA/TS-N (HMMPFAM)
P54725 .....nenlaan llsqnf ~ ~~~~
P32628 .....neaaani lfsdha ~ ~~~~

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- 1) Transmittal Form / 1 Page (1 copy)
- 2) Non-Fee Amendment After Final Action / 8 Pages (1 copy)
- 3) Appendix C / 36 Pages (1 copy)

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